Association of Nonmelanoma Skin Cancer with Second Malignancy

The Women's Health Initiative Observational Study

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The research on which this publication is based was performed pursuant to Contract No. N01-WH-32108 with the National Institutes of Health, Department of Health and Human Services.

The authors acknowledge the following Women's Health Initiative Investigators: Program Office: Barbara Alving, Jacques Rossouw, and Linda Pottern (National Heart, Lung, and Blood Institute, Bethesda, Maryland).

Clinical Coordinating Center: Ross Prentice, Garnet Anderson, Andrea LaCroix, Ruth E. Patterson, and Anne McTiernan (Fred Hutchinson Cancer Research Center, Seattle, WA); Sally Shumaker and Pentti Rautaharju (Wake Forest University School of Medicine, Winston-Salem, NC); Evan Stein (Medical Research Labs, Highland Heights, KY); Steven Cummings (University of California at San Francisco, San Francisco, CA); John Himes (University of Minnesota, Minneapolis, MN); and Bruce Psaty (University of Washington, Seattle, WA).

Clinical Centers: Sylvia Wassertheil-Smoller (Albert Einstein College of Medicine, Bronx, NY); Jennifer Hays (Baylor College of Medicine, Houston, TX); JoAnn Manson (Brigham and Women's Hospital, Harvard Medical School, Boston, MA); Annlouise R. Assaf (Brown University, Providence, RI); Lawrence Phillips (Emory University, Atlanta, GA); Shirley Beresford (Fred Hutchinson Cancer Research Center, Seattle, WA); Judith Hsia (George Washington University Medical Center, Washington, DC); Rown Chlebowski (Harbor-University of California–Los Angeles Research and Education Institute, Torrance, CA); Cheryl Ritenbaugh (Kaiser Permanente Center for Health Research, Portland, OR); Bette Caan (Kaiser Permanente Division of Research, Oakland, CA); Jane Morley Kotchen (Medical College of Wisconsin, Milwaukee, WI); Barbara V. Howard (MedStar Research Institute/Howard University, Washington, DC); Linda Van Horn (Northwestern University, Chicago/Evanston, IL); Henry Black (Rush-Presbyterian St. Luke's Medical Center, Chicago, IL); Marcia L. Stefanick (Stanford Center for Research in Disease Prevention, Stanford University, Stanford, CA); Dorothy Lane (State University of New York at Stony Brook, Stony Brook, NY); Rebecca Jackson (The Ohio State University, Columbus, OH); Cora Beth Lewis (University of Alabama at Birmingham, Birmingham, AL); Tamsen Bassford (University of Arizona, Tucson/Phoenix, AZ); Maurizio Trevisan (University at Buffalo, Buffalo, NY); John Robbins (University of California at Davis, Sacramento, CA); Allan Hubbell (University of California at Irvine, Orange, CA); Howard Judd (University of California at Los Angeles, Los Angeles, CA); Robert D. Langer (University of California at San Diego, LaJolla/Chula Vista, CA); Margery Gass (University of Cincinnati, Cincinnati, OH); Marian Limacher (University of Florida, Gainesville/Jacksonville, FL); David Curb (University of Hawaii, Honolulu, HI); Robert Wallace (University of Iowa, Iowa City/Davenport, IA); Judith Ockene (University of Massachusetts/Fallon Clinic, Worcester, MA); Norman Lasser (University of Medicine and Dentistry of New Jersey, Newark, NJ); Mary Jo O'Sullivan (University of Miami, Miami, FL); Karen Margolis (University of Minnesota, Minneapolis, MN); Robert Brunner (University of Nevada, Reno, NV); Gerardo Heiss (University of North Carolina, Chapel Hill, NC); Lewis Kuller (University of Pittsburgh, Pittsburgh, PA); Karen C. Johnson (University of Tennessee, Memphis, TN); Robert Brzyski (University of Texas Health Science Center, San Antonio, TX); Catherine Allen (University of Wisconsin, Madison, WI); Gregory Burke (Wake Forest University School of Medicine, Winston-Salem, NC); and Susan Hendrix (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI).

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Received July 11, 2003; revision received September 22, 2003; accepted September 25, 2003.

BACKGROUND. Heightened risks of second cancers have been reported in patients with nonmelanoma cancer of the skin (NMSC), but this association has not been studied in a large, ethnically diverse, multigeographic population.

METHODS. This cross-sectional study assessed the association of NMSC with another malignancy in the Women's Health Initiative Observational Study, a study that was conducted in 40 communities throughout the U.S. and involved 93,676 postmenopausal women ages 50–79 years. Cancer history, demographics, and previous and current risk exposures were determined by questionnaire at a baseline examination. Logistic regression was used to assess the association (odds ratio) of a history of NMSC with a history of other (non-NMSC) cancers controlling for age and potential confounding factors. Complete cancer data were available in 92,658 women.

DOI 10.1002/cncr.11874

RESULTS. In age-adjusted analyses, women with a history of NMSC (n = 7554 women) were 2.30 times as likely to report a history of another cancer, other than NMSC, compared with women who had no history of NMSC (95% confidence interval [95% CI], 2.18–2.44). In a subgroup analysis, black women with NMSC had 7.46 times the odds (95% CI, 3.08–18.0) of reporting a second malignancy compared with black women without NMSC.

CONCLUSIONS. This study provides additional evidence of an association between NMSC and another malignancy in a large, multiethnic population. ***Cancer* 2004; 100:130–8.**

KEYWORDS: cancer, ethnicity, nonmelanoma skin cancer, risk.

Nonmelanoma skin cancer (NMSC) is one of the most common malignancies in the U.S., and the clinical prognosis for patients with NMSC generally is regarded as benign.[1,2] However, epidemiologic evidence suggests that individuals with basal cell carcinoma or squamous cell carcinoma of the skin (i.e., NMSC) are at elevated risk for developing other malignancies.[3–15] Two reports from a large cohort of patients with NMSC in the Danish Cancer Registry found that the incidence of other cancers was 15–30% higher than expected compared with the general population.[3,4] In those Danish reports, and in others, it was found that selected cancers were increased particularly after a diagnosis of NMSC, including cancers of the buccal cavity, salivary glands, lung, and cutaneous melanoma as well as lymphoma and leukemia.[3–12,15] It also has been found that mortality rates from noncutaneous cancers were 20–30% greater among individuals who had a history of NMSC compared with individuals without a history of NMSC.[16,17] Therefore, although it is usually believed that NMSC carries a benign prognosis, it may portend the occurrence of both cutaneous and noncutaneous multiple primary cancers. Such linkages may be important for revealing previously unrecognized cancer risks, encouraging new routines of follow-up, and promoting early detection of second primary cancers.

Although several studies utilizing cancer registries[3,4,6,7,11–15] have indicated an increased risk for certain cancers after an initial diagnosis of squamous or basal cell carcinoma, the association has yet to be confirmed in a wide variety of ethnic groups from different geographic locations. The association previously was interpreted with caution because of incomplete information on lifestyle risk factors (smoking, nutrition, sun exposure, latitude of residence, socioeconomic status), family history, medical surveillance bias, and other potentially confounding variables.[18] In an effort to address these gaps, the current study was designed to ascertain whether there is an association between a history of NMSC and a history of other cancers in a large, ethnically and geographically diverse sample of women in the U.S. enrolled in the Women's Health Initiative Observational Study (WHI-OS); in addition, we assessed the impact of potential confounding variables on this association.

MATERIALS AND METHODS

Data were collected from the 93,676 community-dwelling, postmenopausal women enrolled in the WHI-OS at 40 clinical centers distributed widely throughout the U.S. The overall study design of the WHI has been published previously.[19] Informed consent was obtained from all participants. The current analysis incorporates demographics and information on cancer history, smoking, diabetes, diet, exercise, health care, hormone use, family history of cancer, and various other factors derived from responses on questionnaires that were mailed to participants and either completed at home and brought to screening visits at the clinic or completed at the clinic.

At entry into the WHI-OS between 1994 and 1998, each woman reported whether she had ever been diagnosed with cancer and, if so, what specific type(s) of cancer. A woman who reported any cancer other than NMSC was coded as having a history of cancer, women who reported NMSC were coded as such, and women who did not report any cancers were coded as having no history of cancer or NMSC. Nonmissing values for these 2 variables were available for 92,658 women.

The percent of daily caloric intake from fat was determined using a semiquantitative food-frequency questionnaire designed to ascertain dietary intake over the previous 3 months. The Minnesota Nutrient Data System software was used to compute daily energy, fat intake, and other nutrient values. Daily energy intakes < 600 kcal/day or > 5000 kcal/day were considered unreliable; women with these levels had their nutrient values set to missing.

Clinic staff performed interviews regarding the use of hormone replacement therapy (HRT). A woman was classified as a *never-user* of HRT if she did not report ever using estrogen or progesterone pills or

patches for > 3 months. Women who reported using estrogen or estrogen and progesterone combinations (pills or patches) at the age at which they were interviewed were coded as *current users* of HRT. Women who reported use of these drugs for > 3 months but whose reported age at last use was before her age at interview were regarded as *past users* of HRT.

Body mass index was computed using values for body weight and height collected by clinic staff using standardized techniques. Physical activity was calculated using responses to questions concerning frequency, duration, and intensity of participation in physical activities each week and was recorded as the estimated total energy expended per week per kilogram (kcal/week/kg).

Geographic region was defined by location of the clinic that enrolled each participant. Clinics with a latitude > 40 ° north, between 35 ° and 40 ° north, or < 35 ° north were designated as falling in the northern, middle, or southern region, respectively.[20] Data regarding lifelong location of residence were not collected.

Statistical Analysis

The outcome variable for this analysis was history of cancer other than NMSC. Of 7665 women in the sample who reported a history of NMSC, 7554 women also reported whether they had had some other malignancy (1878 women had another malignancy, 5676 women had no other malignancy). Logistic regression was used to determine which covariates significantly altered the odds of reporting a history of cancer other than NMSC. A separate logistic regression was performed for each covariate of interest adjusting for age and ethnicity. To determine the role of history of NMSC in predicting history of any other cancer, a multivariate model was developed. Covariates were those known or suspected to be associated with NMSC and included age (continuous), ethnicity (dummy variables for black, Hispanic, American Indian/Alaskan Native, Asian/Pacific Islander, and unspecified), HRT use (dummy variables for past use and current use), percent of total calories from fat (dummy variables for 4 levels ranging from ≤ 30% to > 40%), family history of cancer (yes or no), geographic region (dummy variables for middle and northern regions), smoking status (dummy variables for past and current smoking), education (5 levels), diabetes at screening (yes or no), and current medical care provider (yes or no). Although current medical care provider was not significant in the age-adjusted and ethnicity-adjusted model, it was included in the final multivariate model to adjust for any possible bias related to medical surveillance. A stepwise regression yielded the same model minus education. Complete data for all covariates were available for 82,728 women. Interactions between all covariates and history of NMSC also were evaluated. The addition of interaction terms for each ethnicity with history of NMSC provided race-specific estimates for the effect of NMSC history on the odds of other cancer history. Analyses were performed using SAS statistical software (version 8.01; SAS Inc., Cary, NC).

RESULTS

Of the 92,658 women enrolled in the WHI-OS for whom complete cancer history was reported, 7554 women reported NMSC. Complete data on all pertinent variables were available on 7010 of these individuals. Baseline descriptive characteristics, according to NMSC histories, are shown in Table 1. This cross-sectional study of postmenopausal women spans a broad age range, includes multiple ethnic groups, and involves a generally well educated cohort. Other baseline factors relevant to cancer risk are shown in Table 1 and are presented for descriptive purposes.

Overall, women who reported that they had NMSC had 2.30 times the odds of reporting another cancer other than NMSC compared with women of the same age who had not had NMSC (95% confidence interval [95% CI], 2.18–2.44) (Table 2). The relation between a history of NMSC and a history of other cancer was not restricted to a few specific cancers. Rather, an association with many diverse types of cancers occurred in statistically significant excess, including malignancies of the breast (odds ratio [OR], 2.09; n = 831 women); ovaries (OR, 2.01; n = 98 women); endometrium (OR, 2.0; n = 264 women); colon, rectum, bowel, or intestine (OR, 1.68; n = 124 women); thyroid (OR, 2.60; n = 94 women); cervix (OR, 1.92; n = 165 women); skin (melanoma; OR, 3.29; n = 299 women); liver (OR, 5.96; n = 10 women); lung (OR, 3.43; n = 56 women); brain (OR, 2.12; n = 9 women); bone (OR, 2.90; n = 13 women); and stomach (OR, 1.63; n = 12 women) as well as leukemia (OR, 3.58; n = 24 women), lymphoma (OR, 2.73; n = 42 women), Hodgkin disease (OR, 5.69; n = 17 women), and other malignancies (OR, 2.26; n = 209 women) (Table 2). In the largest racial subgroup (black women), several individual cancers were increased significantly in women who reported NMSC compared with women who did not report NMSC. These included breast cancer (P = 0.007), ovarian cancer (P < 0.001), endometrial cancer (P = 0.015), and cervical cancer (P = 0.03). Other cancer sites were not increased in black women with a history of NMSC (data not shown).

Factors potentially related to a second cancer after age and ethnicity adjustment were examined in the

TABLE 1
Descriptive Characteristics of Observational Study Participants

	NMSC ever					
	No		Yes		All women	
Characteristic	No.	%	No.	%	No.	%
Age group at screening (yrs)						
50–59	27920	32.8	1539	20.4	29459	31.8
60–69	37327	43.9	3447	45.6	40774	44.0
70–79	19857	23.3	2568	34.0	22425	24.2
Ethnicity						
White	69857	82.1	7376	97.6	77233	83.4
Black	7506	8.8	20	0.3	7526	8.1
Hispanic	3483	4.1	60	0.8	3543	3.8
American Indian	394	0.5	17	0.2	411	0.4
Asian/Pacific Islander	2642	3.1	18	0.2	2660	2.9
Other/unspecified	1222	1.4	63	0.8	1285	1.4
Education						
< 12 yrs	4563	5.4	177	2.3	4740	5.1
HS diploma/GED	14011	16.6	956	12.7	14967	16.3
School after HS	30908	36.6	2641	35.2	33549	36.5
College degree or higher	34916	41.4	3731	49.7	38647	42.1
Family income						
≤ $19,999	12945	16.4	861	12.3	13806	16.1
$20,000–$49,999	34147	43.3	3110	44.4	37257	43.4
≥ $50,000	31772	40.3	3029	43.3	34801	40.5
Marital status						
Never married	3993	4.7	343	4.6	4336	4.7
Divorced/separated/widowed	28187	33.3	2443	32.5	30630	33.2
Presently married/living as married	52505	62.0	4735	63.0	57240	62.1
Body mass index						
< 25 kg/m^2	34888	41.0	3618	47.9	38506	41.6
≥ 25 kg/m^2	50216	59.0	3936	52.1	54152	58.4
Smoking status						
Never smoked	42937	51.1	3671	49.2	46608	51.0
Past smoker	35738	42.5	3391	45.4	39129	42.8
Current smoker	5332	6.3	405	5.4	5737	6.3
Current health care provider						
No	4451	5.3	271	3.6	4722	5.1
Yes	79825	94.7	7218	96.4	87043	94.9
HRT usage status						
Never used	34868	41.0	2815	37.3	37683	40.7
Past user	12572	14.8	1296	17.2	13868	15.0
Current user	37590	44.2	3435	45.5	41025	44.3
Geographic region by latitude						
Southern: < 35 ° N	26778	31.5	2814	37.3	29592	31.9
Middle: 35–40 ° N	23322	27.4	2159	28.6	25481	27.5
Northern: > 40 ° N	35004	41.1	2581	34.2	37585	40.6
Family history of any cancer						
No	27595	33.9	1956	26.9	29551	33.3
Yes	53767	66.1	5325	73.1	59092	66.7
Female relative had breast ca						
No	65168	80.9	5517	77.2	70685	80.6
Yes	15343	19.1	1631	22.8	16974	19.4

NMSC: nonmelanoma skin cancer; HS: high school; GED: general education diploma; HRT: hormone replacement therapy; ca: carcinoma.

TABLE 2
Prevalence and Odds of History of Other Malignancies by Nonmelanoma Skin Cancer History Status at Enrollment

	Reported ever having NMSC						
	No (n = 85,170)		Yes (n = 7665)				
Other history of malignancy	No.	%[a]	No.	%[a]	OR	95% Wald confidence limits	P value
Any other cancer (excluding NMSC)	9927	11.66	1878	24.86	2.30	2.18–2.44	< 0.0001
Breast	4444	5.22	831	10.91	2.09	1.93–2.26	< 0.0001
Ovary	540	0.63	98	1.29	2.01	1.61–2.50	< 0.0001
Endometrium	1302	1.53	264	3.47	2.00	1.74–2.29	< 0.0001
Colon, rectum, bowel, or intestine	727	0.85	124	1.63	1.68	1.38–2.04	< 0.0001
Thyroid	401	0.47	94	1.24	2.60	2.07–3.28	< 0.0001
Cervix	1030	1.21	165	2.17	1.92	1.62–2.28	< 0.0001
Melanoma	885	1.04	299	3.93	3.29	2.87–3.76	< 0.0001
Liver	25	0.03	10	0.13	5.96	2.71–13.11	< 0.0001
Lung	162	0.19	56	0.74	3.43	2.51–4.69	< 0.0001
Brain	43	0.05	9	0.12	2.12	1.02–4.39	0.0429
Bone	51	0.06	13	0.17	2.90	1.55–5.44	0.0009
Stomach	47	0.06	12	0.16	3.17	1.63–6.18	0.0007
Blood (leukemia)	64	0.08	24	0.32	3.58	2.21–5.80	< 0.0001
Bladder	168	0.20	23	0.30	1.26	0.81–1.95	0.3114
Lymphoma	163	0.19	42	0.55	2.73	1.92–3.86	< 0.0001
Hodgkin disease	37	0.04	17	0.22	5.69	3.12–10.39	< 0.0001
Other	979	1.17	209	2.89	2.26	1.94–2.64	< 0.0001

NMSC: nonmelanoma skin cancer; OR: odds ratio.
[a] Percentages were based on women with a nonmissing response for the cancer in question who reported no history of nonmelanoma skin cancer (NMSC) and reported a history of NMSC, respectively.

7665 women who reported a history of NMSC (Table 3). The odds of reporting a history of another cancer were related significantly to ethnicity, age at screening, geographic region by latitude, HRT use status, percent of total calories from fat, family history of any cancer, and family history of breast cancer. All of these were associated with increased odds for a second cancer over the referent group, except for current HRT use and geographic region. Living in the middle or northern latitude regions was associated with reduced odds for other cancers over the southern region referent group. Factors that were identified as unrelated to risk of a second cancer after age and ethnicity adjustment were family income, marital status, education, body mass index, smoking status, alcohol intake, coffee intake, supplement use, having a current health care provider, total expenditure from physical activity, years lived or worked on a farm, and months spent working in the yard (data not shown).

Among women who did not report having had NMSC, the probability of reporting another cancer was relatively consistent across geographic regions. However, among white women who reported having NMSC, the probability of another cancer decreased sharply for women in the middle region and decreased slightly more for women in the northern region compared with women in the southern region (Table 3). The geographic region variable was significant in models that predicted the prevalence of cancer histories among white women with history of NMSC but was not significant among black women with history of NMSC.

We also analyzed the relation between a history of NMSC and a history of another cancer within ethnic/racial groups (Table 4). A white woman with a history of NMSC had an odds of reporting another malignancy that was 2.27 times (95% CI, 2.15–2.41) that of a white woman of the same age without a history of NMSC. In multivariate adjustment, the OR was 2.25 (95% CI, 2.11–2.39), adjusting for age, ethnicity, HRT use status, percent calories from fat, family history of cancer, geographic region, smoking status, education status, diabetes at screening, and medical care. Black women with a history of NMSC had an odds of reporting a history of another malignancy that was 7.46 times (95% CI, 3.08–18.0) that of black women of the same age without a history of NMSC. The OR was 7.14 in the multivariate adjusted model. Hispanics (OR, 3.67), American Indians (OR, 4.51), and Asian/Pacific Islanders (OR, 5.64) who had a history of NMSC all had greater odds of reporting another cancer compared with their counterparts who had no history of NMSC. However, the 95% CI for all ethnicities other than black overlapped the confidence interval for whites.

TABLE 3
Odds Ratios, Adjusted for Age and Ethnicity, Relating Various Covariates to History of Another Malignancy in Women with a History of Nonmelanoma Skin Cancer

Independent variable of interest	OR	95% Wald confidence limits	*P* value
Age group at screening (yrs)[a]			
50–59	1.00	NA	NA
60–69	1.26	1.09–1.46	0.0021
70–79	1.69	1.45–1.96	< 0.0001
Ethnicity[b]			
White	1.00	NA	NA
Black	3.34	1.38–8.08	0.0075
Hispanic	1.23	0.70–2.17	0.4754
American Indian	2.04	0.77–5.40	0.1519
Asian/Pacific Islander	1.49	0.56–3.99	0.4272
Unspecified	0.85	0.47–1.54	0.5856
Diabetes at screening			
No	1.00	NA	NA
Yes	1.37	1.05–1.80	0.0224
HRT usage status			
Never used	1.00	NA	NA
Past user	1.34	1.16–1.54	< 0.0001
Current user	0.53	0.47–0.59	< 0.0001
Geographic region by latitude			
Southern: < 35 ° N	1.00	NA	NA
Middle: 35–40° N	0.86	0.75–0.97	0.0186
Northern: > 40° N	0.80	0.71–0.91	0.0005
Percent of total calories from fat			
≤ 30%	1.00	NA	NA
30–35%	1.27	1.11–1.46	0.0007
35–40%	1.30	1.11–1.51	0.0008
> 40%	1.38	1.18–1.62	< 0.0001
Family history of any cancer			
No	1.00	NA	NA
Yes	1.19	1.06–1.35	0.0049
Female relative had breast ca			
No	1.00	NA	NA
Yes	1.20	1.06–1.37	0.0036

OR: odds ratio; NA: not available; HRT: hormone replacement therapy; ca: carcinoma.
[a] Adjusted for ethnicity.
[b] Adjusted for age.

The OR for black women with NMSC was greater than that for white women with NMSC, and the 95% CI for black women lies entirely above that for white women. White and black ethnicities with NMSC showed a significant difference in the odds of reporting another cancer. However, among women who did not report having NMSC, there was no difference between the two ethnicities in the odds of reporting another cancer.

DISCUSSION

This cross-sectional study, which was undertaken in a large, ethnically diverse, and clinically well characterized sample, supports an association between a history of NMSC and a history of other cancers in women. Increased cancer risk was found in all age groups studied (ages 50–79 years) across different ethnic backgrounds, in women living in different latitudes in the U.S., in women with higher and lower educational backgrounds, in those with high or low body mass index, in smokers, and in never smokers.

NMSC is the most common type of skin cancer among the white population in the U.S., but population-based studies are rare. Because hospitalizations are not required, and prognosis usually is considered favorable, these cancers (especially basal cell carcinoma) have not been recorded routinely in most cancer registries.[1,2] Unlike population-based cancer registries in the U.S., the Danish Cancer Registry has recorded NMSC since 1978. Utilizing these data, Frisch and colleagues reported a higher incidence of subsequent primary cancers in Danish men and women with both squamous and basal cell skin carcinomas compared with the incidence in the general Danish population.[3,4] Whether these data can be extrapolated to other populations has not been confirmed. In the current study, we found that the association of NMSC and other cancers was strong in whites and apparently stronger in blacks. The black cohort was large enough to demonstrate a significant difference from whites, but other nonwhites showed a similar trend. Thus, the association appears to relate to various racial groups, including whites and nonwhites.

Previous studies of this correlation[3,4] were unable to address important potential confounding factors, such as lifestyle variables and medical surveillance bias, which may account for some or all of the association.[3,4,18] In the current study, extensive data were available from the WHI-OS, including HRT use, percent of dietary calories from fat, family history of cancer, geographic region, smoking status, education, diabetes status, and access to medical care. Controlling for medical surveillance seems especially important given the univariate relation of current medical care provider with NMSC (Table 1) and the possibility of response bias. However, after adjustment for this and the other factors, a strong relation between a history of NMSC and a history of other malignancies remained, indicating that it is unlikely that the relation is explained by these confounding factors. Thus, this study strengthens the evidence that the association is not due to confounding by these variables.

The current study relied entirely on self-report of both NMSC and other cancers, and validity of self-report of cancer within this study has not been assessed. However, several previous reports from other similar studies suggest that self-reported cancer diag-

TABLE 4
Age-Adjusted and Multivariate-Adjusted Odds Ratios Relating History of Nomelanoma Skin Cancer to History of Another Malignancy by Ethnicity

	Age adjusted			Multivariate adjusted[a]		
Ethnicity	OR	95% Wald confidence limits	*P* value	OR	95% Wald confidence limits	*P* value
White	2.27	2.15–2.41	< 0.0001	2.25	2.11–2.39	< 0.0001
Black	7.46	3.08–18.04	< 0.0001	7.14	2.66–19.15	< 0.0001
Hispanic	3.67	2.06–6.53	< 0.0001	3.00	1.52–5.90	0.0015
American Indian	4.51	1.63–12.50	0.0038	4.79	1.57–14.63	0.0060
Asian/Pacific Islander	5.64	2.09–15.24	0.0006	6.80	2.34–19.74	0.0004

OR: odds ratio.
[a] Adjusted for age, ethnicity, hormone replacement therapy use, percent of total calories from fat, family history of any cancer, geographic region, smoking status, education, diabetes at screening, and current medical care provider.

nosis is reasonably accurate. For example, Colditz et al. reported from the Nurses Health Study that > 90% of self-reported cases of cancers of the breast, skin, large bowel, and thyroid were confirmed by histopathology reports.[21] The reliability of self-reported cancers of the lung, ovary, and uterus were lower in that study. In a study of community-dwelling men and women that resembled more closely the general population in this study, Bergmann et al. reported a sensitivity of self-reported cancer at any site versus registry-documented cancer of 0.93.[22] Others have reported similarly impressive reliabilities of self-reports of cancer diagnoses.[23] However, aside from the report of Colditz et al., others apparently have not evaluated the accuracy of NMSC self-report in epidemiologic research. Therefore, although the current study relied only on self-report, prior research strongly supports a high rate of agreement of self-report with actual diagnosis of cancer other than NMSC. In addition, it seems unlikely that self-report of non-NMSC would be reported in a differential manner by postmenopausal women with or without a history of NMSC. Thus, we do not consider that this limitation is a likely explanation for the high ORs observed here.

This study was cross-sectional and could not establish a temporal relation between NMSC and other cancers, as cancer registries may.[3,4,6,9,10,12–15] A supplementary analysis of a Danish cohort showed no difference in risk of subsequent cancer for those with a first basal cell carcinoma compared to the entire basal cell skin carcinoma cohort.[4] Those results suggested that cancer or treatment of cancer before the basal cell carcinoma of the skin developed had no demonstrable effect on the subsequent cancer risk.[4] Thus, whereas the current study could not establish a temporal relation between NMSC and second malignancy, the previous Danish work, as well as others, suggests this link.[13–15] The current study also was limited to observations in postmenopausal women only. Therefore, further confirmation of this association in men is warranted.

For whites in the U.S., the incidence of NMSC is associated most strongly with age and lifelong residence in areas with high levels of ambient ultraviolet B (UVB) radiation (i.e., lower latitudes).[1,2,24,25] In the current study, white women who had a history of NMSC currently living in the southern latitudes had a 20% greater odds of having a history of another cancer compared to white women who had a history of NMSC living in northern latitudes. Black women who had a history of NMSC, however, showed no geographic region variation regarding risk of other cancers. It is noteworthy that the geographic region did not impart an increased risk for other cancers among white or black women without NMSC. To assess whether the excess of other cancers among white women with NMSC in southern latitudes was due to melanoma (acknowledged to be due primarily to solar radiation exposure), we investigated regional risk variation with melanoma removed from the outcome variable. The estimated OR for all other cancers did not appear sensitive to the inclusion or exclusion of melanoma.

A number of potential mechanisms may account for the association noted here. Exposure to sunlight is a major risk factor for both squamous and basal cell carcinoma of the skin.[2,24,25] Moderate levels of UV irradiation of the skin can cause local and systemic immune suppression, including cellular suppression of cell-mediated immunity.[26–29] Reduced DNA repair capacity of T-lymphocytes correlates with the development of basal cell skin carcinoma in patients who are overexposed to UVB.[30] UV-induced *p53* suppresser gene mutations play a role in > 50% of squamous

cell carcinomas of the skin.[1,31,32] Mutations in *p53* occur in about 50% of all malignancies. In addition, *p53* is essential for up-regulation of Fas molecules, which are important in regulating cellular senescence and apoptosis.[32] UV light dysregulation of Fas also is implicated in skin cancers.[32] A predisposition to a *p53* mutation, or reduced DNA repair capacity, may be the common etiologic factor for development of both a NMSC and a second malignancy. Whereas excessive sun exposure in predisposed individuals may explain the development of NMSC alone, for the development of other malignancies also to occur, UV light and/or other interacting etiologies, such as viruses, may be required to impart broader immunologic disturbances.[26–29,33] For example, the host of acquired immunodeficiency syndrome-related malignancies point to virally induced acquired immunologic deficiencies involved in carcinogenesis.[34,35]

Other common mechanisms of immunosuppression have been linked to the development of skin cancer and other malignancies. Immunocompromised individuals, such as organ transplantation recipients on immunosuppressive therapy, experience increased incidences of NMSC as well as other malignancies such as lymphomas.[2,24,34,35] The elevated production of type 2 cytokines and the concomitant reduction of type 1 cytokines have been reported in patients with NMSC, lymphoma, renal cell carcinoma, glioma, melanoma, pancreatic and gastric adenocarcinoma, bronchogenic carcinoma, and human papillomavirus-associated cervical intraepithelial carcinoma.[1,33] The nevoid basal cell carcinoma syndrome is an autosomal-dominant disorder that results in an increase in other malignancies, such as medulloblastomas. It is believed that the mechanism is to be due to mutation of a tumor suppressor gene, the *patched* gene (9q22 mutation). Mutations in the *patched* gene also have been found in sporadic medulloblastomas, breast carcinomas, meningiomas, and one colon carcinoma cell line.[2,24,35,36] It is noteworthy that striking similarities are observed in basic immunologic defects that favor the development of neoplastic conditions that appear to be unrelated etiologically.

This investigation offered the opportunity to study women of various races, including those of darker pigment who are not considered high risk for developing NMSC (i.e., Black, Hispanic, Asian).[2,20,34,37,38] A new observation in this study, that black women who have a history of NMSC may be at even greater relative risk for reporting another cancer compared with white women who have NMSC, may reflect underlying ethnic immunologic differences. This may be a fruitful area for further research on ethnic-related cancer differences. Ideally, the observations reported here should be examined in future prospective studies.

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